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Stepped care vs. matched care for mood and anxiety disorders: a randomized trial in routine practice

van Straten A, Tiemens B, Hakkaart L, Nolen WA, Donker MCH.
Stepped care vs. matched care for mood and anxiety disorders: a
randomized trial in routine practice.

Objective: The effectiveness of two versions of stepped care [with either brief therapy (BT) or cognitive behavioural therapy (CBT) as a first step] is studied in comparison with the traditional matched care approach (CAU) for patients with mood and anxiety disorders.

Method: A randomized trial was performed in routine mental health care in 12 settings, including 702 patients. Patients were interviewed once in 3 months for 18–24 months (response rate 69%).

Results: Overall, patients' health improved significantly over time: 51% had achieved recovery from the DSM-IV disorder(s) after 1 year and 66% at the end of the study. Respectively, 50% and 60% had 'normal' SCL90 and SF36 scores. Cognitive behavioural therapy and BT patients achieved recovery more often than CAU patients (ORs between 1.26 and 1.48), although these results were not statistically significant.

Conclusion: Stepped care, with BT or CBT as a first step, is at least as effective as matched care.

**A. van Straten¹, B. Tiemens²,
L. Hakkaart³, W. A. Nolen⁴,
M. C. H. Donker⁵**

¹Trimbos-institute, Utrecht and Department of Clinical Psychology, Vrije Universiteit, Amsterdam, ²de Gelderse Roos Institute for Professionalization, Renkum, ³Institute of Health Policy and Management, Erasmus Medical Centre, Rotterdam, ⁴Department of Psychiatry, University Medical Center Groningen, Groningen and ⁵Department of Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Key words: mood disorders; depressive disorder; anxiety disorders; psychotherapy; brief psychotherapy; cognitive therapy; delivery of health care

A. van Straten, Department of Clinical Psychology, Vrije Universiteit Amsterdam, FPP, Van der Boechorststraat 1; 1081 BT Amsterdam, The Netherlands.
E-mail: a.van.straten@psy.vu.nl

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Significant outcomes

- Patients' health improved significantly although at least one-third still suffered from a DSM-IV disorder at the end of the study.
- Stepped care, with either brief therapy (BT) or cognitive behavioural therapy (CBT) as a first step, is at least as effective as matched care.
- Stepped care with BT as a first step is more efficient for the mental health centre than matched care.

Limitations

- About a quarter of all patients did not start with (the assigned) treatment.
- We have no information on the actual therapeutic approaches/techniques used in the three treatment arms.

Introduction

In the Netherlands, the 1-year prevalence for DSM-IV mood and anxiety disorders is estimated to be 7.6% and 12.4%, respectively (1), and the

co-morbidity between these two is known to be high (2, 3). Mental health care for these disorders is usually provided in out-patient Mental Health Centres (MHCs). Care as usual (CAU) consists of a 'matched care' approach in which a multidisciplinary

nary team matches client and therapy, based on intake information about the specific problems and patient characteristics. As a result, the treatment may vary (e.g. interpersonal, supportive, psycho-analytical, eclectic, with or without medication), the intensity may vary, as well as the setting (individual, with family or in a group). In this traditional mental health-care approach several problems are encountered. Firstly, the long waiting lists for CAU indicate a significant gap between the demand for psychological therapy and the available supply. Secondly, we have reason to believe that the percentages of patients receiving evidence-based interventions is low, being comparable with the percentages as described in the international literature (4, 5).

Introducing a stepped care model may increase effectiveness as well as efficiency of mental health care. In a stepped-care model, all patients start with an evidence-based treatment of low intensity as a first step. Progress is monitored and those patients, who do not respond adequately, will 'step up' to a subsequent treatment of higher intensity. Although, this model seems promising, the effectiveness of such a stepped-care model has not been proven yet, as direct comparisons with CAU, i.e. in the Netherlands a matched care approach, is lacking (6).

Aims of the study

The aim of this study is to provide such a comparison. A traditional matched care approach (CAU) is compared with i) a stepped-care model with brief therapy (BT) as a first step and ii) a stepped care model with cognitive behavioural therapy (CBT) as a first step.

Material and methods

With this trial, we aimed at resembling 'routine' care as closely as possible. We specifically chose not to study stepped care in a research setting with top level therapists within a homogeneous sample of patients. Instead, we chose to study the effectiveness of stepped care as it will appear after implementation in 'routine' care. Therefore, the study was performed in MHCs, which normally provide mental health care, with therapists with average qualifications, and with patients who normally present themselves at the MHC's (with mild to severe mood and anxiety disorders and with or without psychiatric and/or somatic co-morbidity).

Inclusion of patients

Dutch out-patient mental health care is provided by 47 regional mental health care centres (MHCs).

A representative sample of seven MHCs participated in this study at 12 different settings. Both large and small centres in urban and rural regions were included.

Patients were enrolled in two steps (Figure). Firstly, all patients between 18 and 65 years old who were in need of mental health care, were screened during the inclusion period (February 2000–October 2001) on exclusion criteria: psychotic or manic symptoms, cognitive impairments such as dementia or mental retardation, illegal hard drug dependence (patients with alcohol dependence were not excluded), high suicide risk, or poor command of the Dutch language. The remaining patients were then screened for the presence of mood and/or anxiety disorders with the INSTEL screen, which is a Dutch modified version of the Goldberg-screen (7, 8). Second, all remaining patients were interviewed at home (baseline assessment) by a trained research assistant to determine the presence of mood- and/or anxiety disorders with the composite international diagnostic interview (CIDI). The CIDI, a structured interview developed by the World Health Organization (9, 10), enables trained lay interviewers to assess psychiatric diagnoses according to the DSM-IV. Patients with the following DSM-IV diagnosis were included: major depressive disorder (single episode or recurrent), dysthymic disorder, panic disorder (with or without agoraphobia), social phobia, or generalized anxiety disorder, including co-morbid diagnoses. All eligible patients were asked to participate in the study. After full explanation of the study, 702 patients gave written informed consent (Fig. 1). The first patient started treatment in March 2000. Data collection ended in July 2003, although 26 patients were still in treatment at that time.

Assignment and masking

As the study took place in routine settings, we had to take into account the existing treatment capacity in the 12 chosen settings, which led to the following scheme: at six settings CAU vs. CBT was studied, at three settings CAU vs. BT was studied, at two settings BT vs. CBT was studied and at one setting all three treatments were studied simultaneously. We made sure that each treatment was carried out in six different MHC's. We used block randomization ($n = 4$, or 6 when randomized to three conditions), stratified by MHC setting. The randomization scheme was derived by computer and managed centrally. When a patient was included, the researchers opened an envelope and the randomization outcome was reported to the

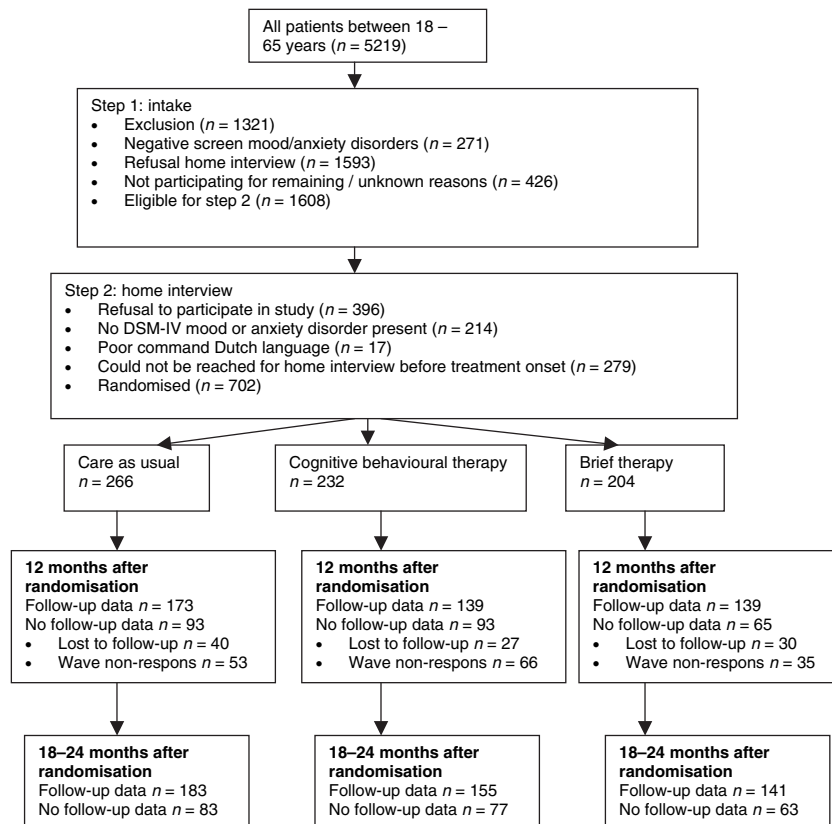


Fig. 1. Patients included in the study.

MHC. Patients and therapists were informed about the randomization outcomes, but the research assistants who performed the interviews were kept blind during the whole study. Power analysis with an expected difference in outcome between Matched Care and either one of the Stepped Care approaches of 15%, and the usual $\alpha = 0.05$ and $(1-\beta) = 0.80$, prompted us to aim for inclusion of 750 patients. As the result of slower inclusion rates than expected, we finally included a total of 702 patients: 266 CAU patients, 232 CBT patients and 204 BT patients.

Interventions

The MHCs decided which therapists participated. The requirements were that each therapist would participate in one condition only and that the therapist had to be experienced in the therapy provided. During a 1-day meeting preceding the study with all participating BT therapists, consensus was achieved on a number of core elements of this treatment. These elements were described in a limited protocol in which all therapists were trained for 2 days. The same procedure was followed in the CBT condition. CAU was not protocolized but all therapists were informed about the study in meetings with the researchers.

Brief therapy was introduced in the Netherlands in the '80s as a remedy against the long waiting lists. It rapidly gained popularity and it is currently offered to approximately 20% of all Dutch patients although its effectiveness has never yet been studied (11). It is suitable as a first step in a stepped care model as it is characterized by a quick onset (no waiting lists) and a limited number of sessions (five sessions and two booster sessions within 6 months). In this study, BT was characterized as follows. During the first session a scheme was used to assess the main complaints, the circumstances (social, work, finances etc.), and personal functioning. Based on this scheme, a treatment rationale was defined and a workplan formulated. Between sessions the patients were supposed to perform 'homework'. In BT complaints were defined as problems and patients were learnt how to cope with these problems on their own. Keywords were: creating hope by clarifying the problem and emphasising and strengthening the patients own competencies and coping abilities.

Cognitive behavioural therapy was chosen as a standard treatment. It might also be a suitable first step in a stepped-care model as it is a relatively short treatment (10–15 sessions) and its effectiveness for many types of depressive and several types

of anxiety disorders has been proven (12–15). In this study, CBT consisted of five modules: i) introduction (one session); ii) providing information about the aim and the procedure of the treatment and assessing patients' cognitions (three sessions); iii) changing cognitions by challenging them (three sessions); iv) changing behaviour by performing behaviour experiments while challenging cognitions (three sessions); v) integrating new behaviour in patients' lives by additional behaviour experiments (one to five sessions). All patients were given written information about their disorder, the most frequently occurring automatic thoughts, and ways to challenge these automatic thoughts.

Both BT and CBT were considered as first steps in a stepped-care model. Therefore, all patients were allowed to switch treatments, during or after treatment completion, should either the patient or the therapist be convinced that the clinical effects were insufficient. In other words: patients were allowed to 'step up'. Furthermore, severely ill patients in all three treatment conditions were allowed to receive antidepressant medication in addition to the psychological treatment. The prescription was protocolized in accordance with current Dutch guidelines.

Outcome assessments

Patients were interviewed at baseline and then every 3 months irrespective of waiting times for treatment or treatment duration. Baseline assessment, 1-year follow-up and the last follow-up were face to face interviews. All other follow-ups were brief interviews (30 min) by telephone. The final follow-up interview was at least 18 months after enrolment in the study. The first patients to enter the study ($n = 64$) could be followed for 24 months, others were followed for 21 months ($n = 121$) or 18 months ($n = 299$). In analysis, we controlled for differences in follow-up period.

Various demographics were assessed during the baseline interview (age, gender, educational level, ethnicity, work status (paid job or not) as well as the presence of chronic somatic conditions (16), and the 'Big Five' personality dimensions (NEO-FFI; 17): neuroticism, extraversion, openness to experience, agreeableness and conscientiousness.

The primary outcome was recovery after 12 months and at completion of the study. Recovery was defined as having no current mood or anxiety disorder. Other outcomes were 'severity of symptoms' and 'mental health functioning', both of which were measured during all interviews (face-to-face and telephone). Severity of symptoms was measured with the total score of the 90 items

Symptom CheckList (SCL90; 18). The total score is obtained by adding the item scores, and ranges from 90 (no distress) to 450 (extremely distressed), where 115 (males) and 123 (females) represent the mean scores for the population (18). Mental health functioning refers to the mental component summary score of the Short Form SF36 (19). This score ranges from 0 (poor mental health functioning) to 100 (optimal mental health functioning) where 50 represents the mean score for the population (20).

Attrition

At 12 months, a total of 97 patients were lost to follow-up while another 154 patients were unable to participate in that particular assessment. As a result, the response rate was 64% ($n = 451$). The response rate at the end of the study was 68% ($n = 479$). The reasons for study drop-out varied: many patients could not be reached because they had changed telephone numbers or addresses, others did not want to be reminded of the time that they were depressed or anxious, or experienced the interviews as a burden because of other reasons. Furthermore, a substantial number of patients did not give any reason for drop-out.

There were no statistically significant differences in response rates between the three treatment conditions. Furthermore, we compared the responders with the non-responders on all baseline characteristics. The non-responders were significantly younger than the responders (35.0 vs. 37.1 years, $P < 0.01$, 12 months analyses; 34.5 vs. 37.2 years, $P < 0.01$, 18–24 months analyses), and scored significantly lower on the personality trait agreeableness (mean score 4.1 vs. 4.4, $P = 0.05$, 12 months analyses; mean score 4.1 vs. 4.4, $P = 0.07$, 18–24 months analyses). There were no differences with regard to the DSM-IV mood and anxiety disorders, the SCL90 and the SF36 mental health component score with one exception. The end of study non-responders suffered significantly more often from a mild (single episode) depressive disorder than the responders (15% vs. 10%, $P = 0.05$).

Data analyses

The association between the types of treatment and full recovery was analysed with logistic regression analyses. We controlled for the differences in follow up period (18, 21 or 24 months). The association between the types of treatment and changes in the SCL90 and the SF36 was analysed with generalized estimating equation (GEE)

Characteristics	All patients (<i>n</i> = 702)	CAU (<i>n</i> = 266)	CBT (<i>n</i> = 232)	BT (<i>n</i> = 204)
Male (%)	39	35	41	41
Age [mean (SD)]	36.4 (10.2)	36.1 (10.3)	36.5 (9.9)	36.6 (10.3)
Born in the Netherlands (%)	90	94	86	90
Educational level (% max vocational training)	74	76	76	69
With a paying job (%)	66	62	68	70
Somatic disorders				
With a disorder (%)	67	69	66	66
Using somatic medication (%)	26	30	23	26
Personality traits (mean scores)				
Neuroticism	7.8	7.8	7.8	7.8
Extraversion	3.3	3.2	3.3	3.3
Openness to experience	5.1	5.0	5.4*†	5.0
Conscientiousness	3.1	3.3	3.0	3.0
Agreeableness	4.3	4.4	4.2	4.2
Patients using antidepressants (%)	36	39	35	32
DSM-IV diagnoses (% of patients)‡				
Any mood disorder	88	88	90	88
Depression, single episode, mild	11	12	12	10
Depression, single episode, moderate	15	16	14	13
Depression, single episode, severe	24	23	28†	20
Depression, recurrent, mild	16	14	14	20
Depression, recurrent, moderate	10	10	10	10
Depression, recurrent, severe	11	11	8	12
Dysthymic disorder	27	24	28	28
Any anxiety disorder	53	52	54	53
Panic disorder without agoraphobia	13	13	12	15
Panic disorder with agoraphobia	22	23	21	23
Social phobia	27	26	29	26
Generalized anxiety disorder	4	3	6	3
Mental health functioning (SF36)				
Mean score (SD)	27 (9)	27 (9)	26 (8)†	28 (9)
Within range of normal population (%)	10	10	7†	13
Psychological symptoms (SCL90)				
Mean score (SD)	223 (59)	223 (57)	227 (59)	217 (62)
Within range of normal population (%)	11	11	11	13

CAU, care as usual; CBT, cognitive behavioural therapy; BT, brief therapy.

*Statistical significance in comparison with CAU: $P < 0.05$.

†Statistical significance in comparison with BT: $P < 0.05$.

‡Patients may have more than one diagnosis.

Table 1. Demographics and health status at baseline of 702 studied patients

time-lag models (21). An exchangeable correlation structure was employed. The reported regression coefficients are to be interpreted as the mean differences (in the SCL90 or the SF36 scores) between the treatment conditions over time (i.e. for each assessment we controlled for the score on the previous assessment). Patients with missing baseline values ($n = 60$ for the SCL90 and $n = 66$ for the SF36) could not be analysed with GEE. All other patients were included, despite missing one or more follow-up interviews. There were no significant interaction effects between time and treatment, and therefore all analyses were performed without this interaction term.

All logistic and GEE analyses were performed on both the 'intention to treat' and the completers sample. In the intention to treat sample, all patients were analysed as they were randomized while in the completers sample only patients who

had started with the assigned treatment and finished it (with or without further referral) were included. Of all 702 patients, 414 (59%) were completers (60% of the CAU patients; 56% of the CBT patients; 60% of the BT patients). Finally, all analyses were repeated with missing data being imputed in two ways: i) by carrying the last observation forward and ii) by predicting the missing values by regression analyses on the available data based on all baseline characteristics.

Results

Demographics and health status at baseline

Most patients met the criteria for more than one DSM-IV disorder (Table 1). Of the 702 patients in the study, 41% suffered simultaneously from anxiety and mood disorders, 47% suffered only

Table 2. Characteristics of the way treatments were performed during the study

	CAU (n = 266)	CBT (n = 232)	BT (n = 204)
Start treatment (% of patients)			
Randomized treatment	75	72	71
Other treatment	13‡	15	21*
No show	12	13	8
Days after randomization before start treatment			
Unknown (%)	8	7	4
Mean number of days (SD)	89 (69)	83 (58)	50 (43)*†
Number of sessions			
Unknown (%)	2	3	2
Mean number (SD)	12 (14)	10 (7)	8 (11)*†
Treatment duration			
Unknown (%)	8	7	4
Mean number of days (SD)	265 (232)	223 (180)*	178 (176)*†
Termination of treatment (% of patients)			
Unknown	12	2*	3*
Treatment not yet finished at end of study	7	2*	2*
Mutual agreement	50	55	54
Mutual agreement with referral	10	18*	24*
Dropped out	20	23	17

CAU, care as usual; CBT, cognitive behavioural therapy; BT, brief therapy.

*Statistical significance in comparison with CAU: $P < 0.05$.

†Statistical significance in comparison with CBT: $P < 0.05$.

‡Patients treated with CBT or BT by therapists who were trained in the study protocol.

from (a) mood disorder(s) and 12% only from (an) anxiety disorder(s). Approximately 90% of all patients had SCL90 and SF36 scores outside the range of the normal population and another 5% scored outside the range on either one of these measures. Overall, there were few differences between the three treatment groups at baseline (Table 1).

Treatment characteristics

Of all 702 patients, 11% ($n = 78$) did not show up for treatment (Table 2). Another 16% ($n = 111$) did not start with the assigned treatment, because of administrative errors (e.g. randomization result got lost) or to deliberate decisions of patients or therapists who thought that randomization had led to inappropriate treatment allocation. Patients randomized to BT more often started with another type of treatment (21%) than did patients in the CAU condition (13%; $P = 0.02$). Overall, there were no statistically significant baseline differences between the patients who did not show up, who did not start with the assigned treatment, and who started with the assigned treatment.

The differences between the three treatments were as expected. Brief therapy patients started soonest after randomization (mean 50 days), had

the fewest sessions (mean 8) and the shortest treatment duration (mean 178 days; Table 2). Compared with CAU, these results were all statistically significant, with $P < 0.01$. Patients in the CBT condition also finished therapy within a shorter period of time (mean 223 days) and with fewer sessions (mean 10) than CAU patients ($P = 0.10$ and $P = 0.04$ respectively).

Only 10% of the CAU patients were referred to another treatment (after termination of the first) compared with 18% of the CBT patients ($P = 0.03$) and 24% of the BT patients ($P < 0.01$). This was expected, since both CBT and BT are the first step in a stepped care approach. This also explains why the mean number of sessions for both CBT and BT exceeded the maximum number of sessions as described in the treatment protocols (15 sessions for CBT and seven for BT).

Health outcomes and the association with the treatment conditions

Overall, patients' health improved significantly over time. The SF36 mental health composite score improved from 27 (SD 9) at baseline to 40 (SD 13) after 12 months, and 43 (SD 13) after 18 months. The SCL90 score improved from 223 (SD 59) at baseline to 171 (SD 66) after 12 months and 156 (SD 56) after 18 months. After 1 year, 51% of the patients had achieved full recovery from the DSM-IV mood and anxiety disorders. Of those recovered patients 52% had SF36 and SCL90 scores within the range of the normal population, which is defined as a score of maximally one SD above the population mean (16, 17). At the end of the study, two-thirds (66%) of the patients were recovered from their DSM-IV disorder and 60% of those (40% of all patients) had SF36 and SCL90 scores within the normal range. This means that 1 year after baseline 27% of all patients were fully recovered on all three reported outcomes, a figure that increased to 40% at the end of the study.

Figure 2 shows that both CBT and BT patients more often achieved recovery of the DSM-IV mood and anxiety disorders, at 1 year and at the end of the study, than did CAU patients. Moreover, the SCL90 and SF36 scores of the CBT and BT patients improved more over time than the mental health of the CAU patients. However, all results were statistically non-significant (Table 3). All analyses were repeated after imputation of missing values both with last observation carried forward and with imputation by regression. The effect sizes remained roughly the same (results available at request).

Discussion

This trial performed in daily practice of out-patient MHCs showed that a stepped-care approach, where either BT or CBT is offered as a first step, is at least as effective as a matched-care approach for patients with mild to severe mood and/or anxiety disorders, with and without psychiatric and somatic co-morbidity. The stepped-care approach with BT as a first step was more efficient as significantly fewer sessions were needed to obtain similar treatment results as in the other two approaches. At the end of the study, two-thirds of the patients were recovered from their DSM-IV disorder and 40% of all patients also had SF36 and SCL90 scores within the normal range.

Although there were patients who refused to enter the study, as well as patients who dropped out of the study or the treatment, we could not find indications of selection bias. Firstly, the patients in

our trial reported more (severe) psychological symptoms at baseline (mean SCL90 score 223) than a reference population of arbitrarily chosen Dutch out-patient psychiatric patients (mean SCL90 score 204), implying that our study was not skewed towards the healthier patients. Secondly, apart from a difference on the personality trait agreeableness, we could not demonstrate significant differences with regard to the mental health status between patients who did and did not complete the study. Thirdly, the results on the completer's analyses (patients who started and completed the assigned treatment) were not different from the intention to treat analyses. Lastly, the treatment drop out in our study is comparable with that of other out-patient treatment studies (22, 23), and, even more importantly, to the general Dutch MHC population of patients with a mood or anxiety disorder (5).

The relatively high percentage of patients who were randomized to BT, but received another type of treatment (21%) probably reflects the reluctance of therapists to work with a stepped care model and to offer a minimal intervention to patients. Normally, about 20% of all Dutch MHC patients receive BT. These are preferably patients with mild depressive disorders with a recent onset, and with problems related to personal relations or work (11, 24). It has been shown before that therapists are reluctant to apply BT in the case of personality disorders and symptoms of anxiety (25). Our study shows that it is difficult to fully implement a stepped-care model in routine practice at this moment. Nevertheless, our findings also indicate that the majority of patients (in our study 71%, instead of the usual 20%) with mood or anxiety disorders (including both mild and severe cases, first and recurrent depressions, with and without

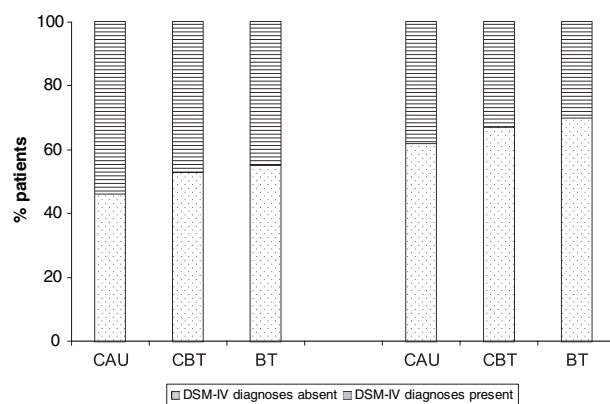


Fig. 2. Recovery in terms of absence of a DSM-IV diagnosis of mood or anxiety disorders, both 12 month after baseline and at the end of the study (18–24 months after baseline).

Table 3. The association between the three types of psychological treatment and the outcomes

Months	CIDI – no anxiety/mood disorder		SF36 – good mental health	SCL90 – many psychological complaints
	T0-12†	T0 –12/18/24†§	T0 to 18‡	T0 to 18‡
ITT				
CAU	1.0 (reference)	1.0 (reference)	0.0 (reference)	0.0 (reference)
CBT	1.36 (0.87–2.12)	1.26 (0.81–1.98)	0.73 (–0.69/2.14)	–2.18 (–4.93/0.57)
BT	1.48 (0.94–2.32)*	1.41 (0.89–2.25)	0.56 (–0.87/1.99)	0.12 (–2.96/3.19)
Treatment completers				
CAU	1.0 (reference)	1.0 (reference)	0.0 reference	0.0 reference
CBT	1.51 (0.86–2.63)	1.21 (0.69–2.14)	1.27 (–0.54/3.08)	–2.27 (–5.79/1.25)
BT	1.65 (0.94–2.89)**	1.79 (0.96–3.34)***	1.41 (–0.34/3.15)	–2.27 (–6.26/1.71)

CAU, care as usual; CBT, cognitive behavioural therapy; BT, brief therapy.

* $P = 0.09$; ** $P = 0.08$; *** $P = 0.07$.

†Values are expressed as OR (95% CI).

‡Values are expressed as β (95% CI); the beta coefficient represents the mean difference over time in the SF36 (score ranges from 0 to 100), and the SCL90 (score ranges from 90 to 450).

§Analyses were corrected for time of assessment.

co-morbidity) may be offered BT because on average there are no negative consequences for the mental health of the patients.

In a review of efficacy and effectiveness of psychotherapy Lambert and Ogles (22) described that in clinical trials, 40–70% of the patients show substantial benefit. The results of our trial fit within this range although our figures are more inclined towards the lower limit: 12 months after baseline about half of all patients had recovered from the mood and anxiety disorders while half of those patients also had psychological health and quality of life scores within the range of the general population. At the end of the study about two-thirds had achieved recovery and almost two-thirds of them had 'normal' psychological health and quality of life scores. The lower limits effects may be caused by our specific choice to perform this trial in daily practice with average qualified therapists and 'normal' MHC patients (many with psychiatric and/or somatic co-morbidity). Most RCT's are performed under more ideal conditions, within university settings and more homogeneous patient groups, and may hence demonstrate larger effects. The finding that about one-third to half of all patients who recovered from the DSM-IV disorder still had SCL90 or SF36 scores below population level is in concordance with other clinical and population studies in which residual effects on functioning after DSM-IV recovery have been demonstrated (26).

We could not demonstrate any statistically significant differences in effectiveness between the treatments because recovery might predominantly be determined by common therapy factors (e.g. talking in a structured way about psychological complaints), characteristics of the therapists (e.g. the ability to establish a high quality working relation with the patient), natural recovery and/or use of antidepressant medication (27–30). This implies that the window for improvement attributed to (differences in) psychological treatments is small. The power of our study was based on a 15% difference in outcomes between Matched Care and either one of the stepped-care approaches. We did not include enough patients to be able to detect the actual 8% difference in recovery rates with statistical significance. Yet, although not statistically significant, all results were in favour of the stepped-care approach. Therefore, we conclude that patients do not necessarily benefit more from matched care with more intensive treatments than from stepped care with a low intensity treatment as a first step. From an efficiency point of view we recommend a stepped care approach with BT as a first step. This is confirmed by our cost-effectiveness analyses (31).

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